Influence of HbA_{1c} and BMI on Lipid Trajectories in Youths and Young Adults With Type 1 Diabetes

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Diabetes Care 2017;40:30–37 | DOI: 10.2337/dc16-0430

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To assess the influence of HbA_{1c} and BMI (measured as BMI *z* score [zBMI]) on LDL, HDL, and non-HDL trajectories as youths with type 1 diabetes age into early adulthood.

RESEARCH DESIGN AND METHODS

Dynamic, retrospective cohort study examining changes in lipid values in 572 youths with type 1 diabetes followed longitudinally for a median of 9.3 years. Through longitudinal modeling, we describe the relationship of HbA_{1c} and zBMI on lipid values as subjects age after adjusting for other relevant factors, including lipid-lowering medication use.

RESULTS

The median number of lipid assessments was 7 (range 2–39). Every 1% increase in HbA_{1c} was associated with an ∼2–6 mg/dL increase in LDL levels, with a greater increase in LDL levels as subjects progressed from prepubertal to postpubertal age ranges. A 1-SD increase in BMI was associated with a mean LDL increase of 2.1 mg/dL when subjects were 10 years old and increased to a mean of 8.2 mg/dL when subjects were 19 years old. The association between changes in HbA_{1c} level and zBMI and changes in non-HDL levels as youths aged were similar to the associations found with LDL. The influence of HbA_{1c} and zBMI on HDL levels was small and not dependent on age.

CONCLUSIONS

Changes in HbA_{1c} level and zBMI modestly impact LDL and non-HDL cholesterol and have greater impacts as children age. Addressing elevations in HbA_{1c} and zBMI as children enter into adolescence and beyond may lead to improvements in lipid levels.

Individuals with type 1 diabetes, and especially those with youth-onset disease, have significantly increased cardiovascular risk relative to the general population (1–3). Although much of this increased risk is attributed to diabetic nephropathy (4,5), cardiovascular disease (CVD) mortality remains elevated even in individuals with type 1 diabetes without renal disease (6,7). A study of the Swedish National Diabetes Register described an adjusted hazard ratio for death from CVD as over four times greater in individuals with type 1 diabetes than in individuals in the general population. Even in individuals with target glycemic control ($HbA_{1c} \leq$ 6.9%), the risk of dying from CVD was twice that of the general population, suggesting the need to address nonglycemic CVD risk factors (7). Because of this increased

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Received 26 February 2016 and accepted 28 September 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0430/-/DC1.

cardiovascular risk, the American Diabetes Association, American Heart Association, and National Heart, Lung, and Blood Institute guidelines recommend more aggressive management of elevated LDL cholesterol levels in youths with type 1 diabetes versus youths without type 1 diabetes (8–10).

Recent studies (11–13) have documented suboptimal management of dyslipidemia in youths with type 1 diabetes. Initial approaches for the treatment of dyslipidemia in youths with type 1 diabetes generally include improving glycemic control, dietary changes, and weight loss in overweight and obese youths. One study of a large cohort of youths with type 1 diabetes describes only modest reductions in LDL cholesterol levels with substantial improvements in HbA_{1c} levels in youths over a 2-year period (14), documenting the challenge of targeting glycemic control in order to lower LDL levels.

Trajectories of lipid levels in youths with type 1 diabetes as they age from childhood into young adulthood warrant careful study in order to inform clinical guidelines and practice. Deepening the understanding of the influence of the modifiable risk factors HbA_{1c} and weight status on lipid trajectories, and whether changes in HbA_{1c} and weight status have differential effects on lipid levels at different stages of childhood and young adulthood could help to inform provider management recommendations for dyslipidemia in youths with type 1 diabetes.

In a dynamic cohort of youths observed for a median of 9.3 years (range 1.0–19.5 years), we aimed to describe the trajectories of LDL, HDL, and non-HDL cholesterol as youths with type 1 diabetes age into young adulthood. Further, we aimed to evaluate the effects of HbA_{1c} and weight status (measured as BMI *z* score [zBMI]) on LDL, HDL, and non-HDL cholesterol levels as this cohort traverses childhood and adolescence and enters into young adulthood.

RESEARCH DESIGN AND METHODS

To be included in this dynamic cohort study, participants must have been previously enrolled in one of five psychoeducational or observational studies (15–18) to allow careful phenotyping of participants with respect to type of diabetes, diabetes duration, and sociodemographic characteristics. For all of these studies, participants were required to be youth with type 1 diabetes and be without major untreated medical or psychiatric comorbidities. Other specific inclusion criteria have been published elsewhere (15–18) but were typical, nonrestrictive criteria for youths participating in observational or family-focused interventions. Data were extracted from paper and electronic medical records for the time before and after formal study participation. The Joslin Diabetes Center institutional review board approved all studies, including separate institutional review board approval for the current study.

For the current study, further restrictions limited the initial observation to the availability of an LDL measurement between the ages of 6 and $<$18 years and a duration of type 1 diabetes of $\geq$0.5 years. The cohort was further restricted to include only youths with at least two LDL observations $\geq$1 year apart. Then, all calculated LDLs with triglycerides that were not reported or $\geq$400 mg/dL were excluded. Data were captured across 2 decades between January 1993 and March 2013.

Outcome Definition and Covariates Included

The primary study outcome was subject-specific longitudinal lipid levels. The covariates included in these analyses were age, sex, race/ethnicity, HbA_{1c}, zBMI, cholesterol-lowering supplement usage, and cholesterol-lowering medication usage.

Clinical Values

Height was measured using a stadiometer until adulthood, and weight was obtained by clinical scale; medical assistants obtained both measurements as a part of routine clinical practice in a standardized manner. zBMI values were calculated from the Centers for Disease Control and Prevention normative values in children and National Health and Nutrition Examination Survey (NHANES) values in adults. The Centers for Disease Control and Prevention provide normative values for zBMI in children based on their age to the closest day (19), and the NHANES data provide normative values in adults based on their age to the closest decade such that all female or males 20–29 years of age have the same normative values (20). Because of this difference in precision for normative values for zBMI according to age, we treat zBMI before age 20 and at age 20 or after separately in our analyses.

Because of the limited number of members of racial and ethnic minorities in our cohort, we categorize race/ethnicity as either white (excluding Hispanic) or nonwhite (including Hispanic).

Lipid-Lowering Medications

Data on medication or supplement use were obtained in a systematic manner by trained research staff by manual review of paper and electronic medical records for any participant with an LDL value $\geq$130 mg/dL at any point during follow-up. Although all medication-treated participants used hydroxymethylglutaryl-CoA reductase inhibitors at some point during follow-up, other medications (e.g., fibrates) were also used in either combination or isolation. Participants taking supplements that are known to affect lipid levels (e.g., plant stanol esters, flaxseed) were also noted in our analyses. We considered a lipid value to have been obtained while receiving treatment with a medication or supplement if the medication or supplement was prescribed before the LDL was obtained and if the chart did not indicate that the patient had stopped taking the medication or supplement.

Laboratory Values

The majority ($>$97%) of laboratory values were obtained at the diabetes center, but a few values were obtained from outside clinical laboratories and manually entered into the data set. The data set consisted of 4,440 laboratory and clinical observations from 572 subjects. LDL was missing for 141 observations, HDL was missing for 12 observations, non-HDL was missing for 19 observations, HbA_{1c} was missing for 44 observations, and zBMI was missing for 57 observations (31 youth and 26 adult observations).

Lipid Measurement

In the Joslin Diabetes Center laboratory in Boston, MA, lipids were measured using a Beckman Synchron CX9 analyzer from 1993 until October 2007; using an Ortho Vitros Chemical System from October 2007 until August 2011; and using a Roche Cobas Integra 800 Chemistry Analyzer from August 2011 through

2013. When the laboratory methodology changed, the clinical laboratory always performed quality checks to ensure consistency in lipid measurements. Standards (or calibrators) remained the same during the follow-up period. LDL values were calculated using the Friedewald formula, as follows: (total cholesterol-HDL) − (triglycerides × 0.20). Beginning in November 2007, a direct LDL was analyzed reflexively when HDL concentration was <35 mg/dL and/or triglyceride concentration was >200 mg/dL. Direct LDL was measured on the same platforms as the other lipid measurements (using the Ortho Vitros Chemical System Analyzer from November 2007 until August 2011, and using the Roche Cobas Integra 800 Chemistry Analyzer from August 2011 until 2013). Calculated LDL levels were excluded when LDL level was measured directly on the same day. For these analyses, LDL, HDL, and non-HDL could be fasting or nonfasting. The majority of the laboratory values are nonfasting because nonfasting lipid measurement is common practice within our department as they exhibit little variability with fasting status (21). The non-HDL level is calculated as total cholesterol − HDL.

HbA_{1c} Measurement

HbA_{1c} level was measured using high-performance liquid chromatography from 1993 until November 2010 (Bio-Rad Variant Hemoglobin Testing System, Tosoh 2+2 Analyzer, and Tosoh G7 HPLC Analyzer). Beginning in November 2010, a turbidimetric inhibition immunoassay using the Roche Cobas Integra 800 Analyzer was used. Reference ranges remained constant at 4.0–6.0% and were consistently calibrated to the Diabetes Control and Complications Trial. Similar to the lipid measurements above, when the HbA_{1c} assay changed, the clinical laboratory performed quality checks and ensured the calibration of methodologies.

Proximate Data Capture

For these analyses, each observation was captured according to the date of the lipid measurements. For some observations, if additional clinical or laboratory data were not available on the date that lipids were measured, the data closest temporally to the date of the lipid measurement were used. For missing HbA_{1c} data, the closest HbA_{1c} measurement within 3 months of a lipid measurement was used. For missing height or weight data, the closest measurements within 1 year of the lipid measurement were used.

Statistical Analysis

Descriptive statistics are given for subject level and measurement level characteristics using frequencies (percentages) for discrete variables and mean (SD) or median (25th to 75th percentiles) for continuous variables, as appropriate for the distribution.

Longitudinal mixed models were fit separately for LDL, HDL, and non-HDL as the dependent variable. Each model adjusted for sex and race/ethnicity. Due to nonlinear effects, age at the time of the measurement was modeled as a cubic polynomial. No deviations from linearity were detected for HbA_{1c} or zBMI. Type 1 diabetes duration or age at onset was not included in the models because of collinearity with age. Random subject-level intercepts and HbA_{1c} slopes were included in the LDL and non-HDL models. The HDL model included random subject intercepts and age slopes because the HbA_{1c} slope did not vary significantly by subject. No other factor was identified with a slope that varied significantly by subject in any of the three models. Models also accounted for autocorrelated errors within each subject.

Modifiable risk factors HbA_{1c}, zBMI, and the use of medications and/or supplements were considered as independent variables and included in the model if $P < 0.05$ or if there was substantial clinical significance. Since *z* scores for BMI were calculated using different methods for children and young adults (see above), separate zBMI slopes were modeled for age (at measurement) of <20 years versus >20 years. To mitigate selection bias for the use of medications, indicator variables were included as independent variables for whether the subject ever used medications during the observation period and for whether the subject was currently using medication at the time of the measurement (time-varying indicator). Similar indicator variables were fit for the use of supplements. Interaction terms were included in the model if they were statistically significant ($P < 0.05$). For models where there was a significant interaction of age with HbA_{1c} and/or zBMI, slope estimates were given for various ages. We also tested whether the interaction between age and/or zBMI differed by sex.

Separate between-subject and within-subject slopes were modeled for HbA_{1c} by including the cluster-averaged value in the model as a covariate (22). Since the objective of this study was to assess modifiable risk factors, the within-subject slope was reported in the regression results. No other factor had significantly different between-subject and within-subject slopes.

Residual values from each model were verified to have an approximately normal distribution. All reported *P* values are two sided. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Cohort Characteristics at First Observation

A total of 572 subjects of the 645 in the data set fulfilled the inclusion criteria for these analyses. At the initial observation, subjects were 54% female and had a mean age of 11.9 ± 2.9 years, with a mean age at type 1 diabetes onset of 7.1 ± 3.4 years, and 34% were overweight or obese. The mean LDL concentration was 95 ± 29 mg/dL, the mean HDL concentration was 55 ± 13 mg/dL, and the mean non-HDL concentration was 115 ± 30 mg/dL (Table 1). At the initial observation, 41% of subjects had an LDL concentration of ≥100 mg/dL, 23% had an HDL concentration of <45 mg/dL, and 40% had a non-HDL concentration of ≥120 mg/dL. The initial HbA_{1c} level was 8.9 ± 1.5% (74 ± 16.4 mmol/mol).

Cohort Characteristics at Last Observation

At the final observation, subjects were 21.7 ± 4.1 years old. The mean LDL concentration was 98 ± 35 mg/dL, the mean HDL concentration was 60 ± 18 mg/dL, and the mean non-HDL concentration was 118 ± 45 mg/dL. At the last observation, 41% of subjects had an LDL concentration of ≥100 mg/dL, 17% had an HDL concentration of <45 mg/dL, and 40% had a non-HDL concentration of ≥120 mg/dL. The last HbA_{1c} level was 8.9 ± 1.7% (74 ± 18.6 mmol/mol). Fifty-five of the 572 (10%) subjects were exposed to

lipid-modifying medications or supplements over the course of follow-up.

Supplementary Table 1 describes the measurement level characteristics for the study.

Relationship Between Unadjusted Lipid Levels and HbA_{1c} or Weight Status

Figure 1*A* and *B* describes the unadjusted associations between LDL and HbA_{1c} or weight status, respectively, as subjects age. Both figures demonstrate a stronger impact of the covariate of interest (HbA_{1c} or weight status) and LDL in older subjects than in younger subjects. Figure 1*C* and *D* describe the unadjusted associations between HDL and HbA_{1c} or weight status, respectively, as subjects age. Supplementary Fig. 1 describes the unadjusted associations between non-HDL and HbA_{1c} or weight status as subjects age.

Table 1—Subject demographics and characteristics (*N* = 572)

	%/Mean ± SD/median (25th, 75th percentile)		Range	
	Initial	Last	Initial	Last
Female sex	54			
Nonwhite	9			
Age at T1D onset (years)	7.1 ± 3.4		0.2–15.0	
Age (years)	11.9 ± 2.9	21.7 ± 4.1	6.1–17.9	10.4–32.1
Diabetes duration	4.8 ± 3.1	14.6 ± 4.8	0.5–13.8	2.4–27.5
Neither medication/supplement usage	90			
Medications usage only	6			
Supplements usage only	2			
Both medication/supplement usage	2			
LDL value (mg/dL)*	95 ± 29	98 ± 35	18–247	12–255
HDL value (mg/dL)	55 ± 13	60 ± 18	22–103	9–140
Non-HDL value (mg/dL)	115 ± 31	118 ± 45	45–303	17–611
Triglycerides (mg/dL)	89 (60, 133)	94 (65, 136)	19–1,331	23–1,167
HbA_{1c} (%)	8.9 ± 1.5	8.9 ± 1.7	5.5–14.6	5.6–16.1
HbA_{1c} (mmol/mol)	74 ± 16.4	74 ± 18.6	37–136	38–152

T1D, type 1 diabetes; *LDL values were available for only 571 subjects.

Relationship Between Adjusted Lipid Levels and HbA_{1c} or zBMI

Table 2 reports the adjusted associations of HbA_{1c} and zBMI with LDL. After adjusting for sex and race/ethnicity, both HbA_{1c} and zBMI have age-dependent effects on LDL trajectories. For every 1% increase in HbA_{1c}, LDL levels increase by ~2–6 mg/dL, with a greater increase in LDL levels as subjects progressed into adulthood. Similarly, for a 1-SD increase in BMI related to age- and sex-specific

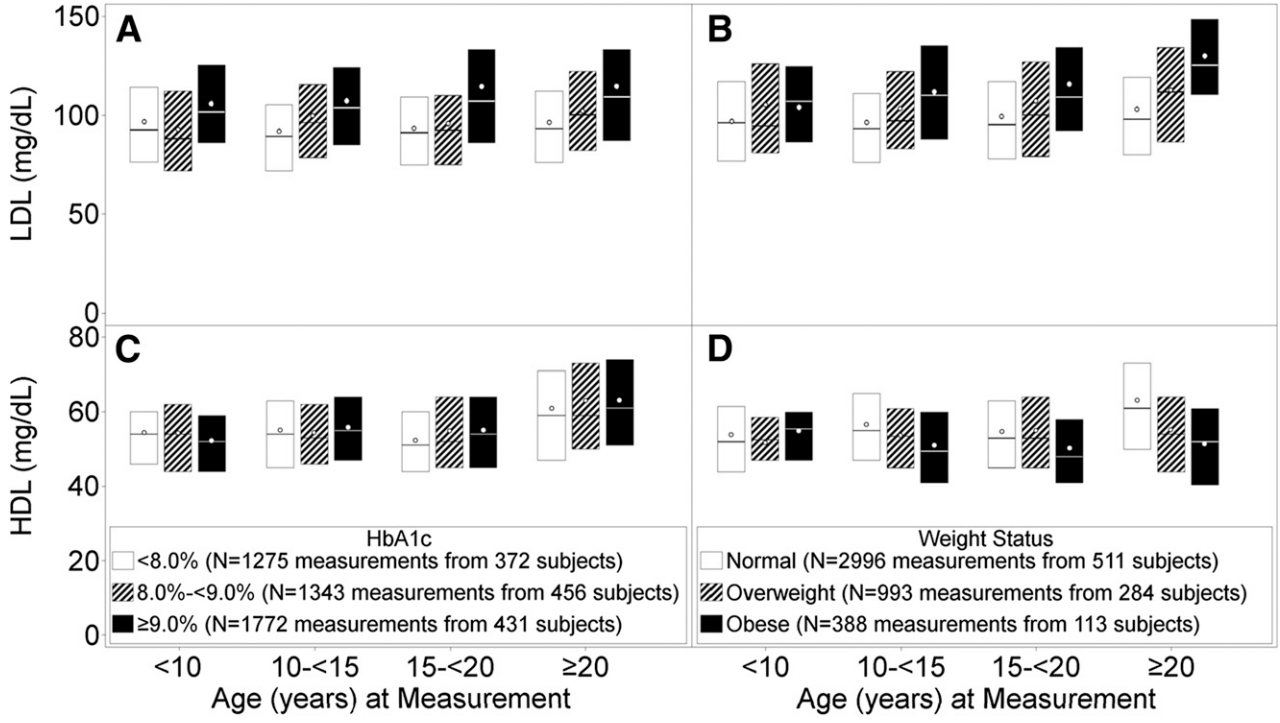

Figure 1—*A*: The distribution of LDL levels according to age-group stratified by HbA_{1c}. *B*: The distribution of LDL levels according to age-group stratified by weight status. *C*: The distribution of HDL levels according to age-group stratified by HbA_{1c}. *D*: The distribution of HDL levels according to age-group stratified by weight status. The horizontal line inside each box indicates the median; the bottom and top of the box indicate the 25th and 75th percentiles, respectively; and the dots indicate the mean. The number of measurements denotes the number where at least one lipid value (LDL, HDL, or non-HDL) is available. The actual number of measurements may be fewer for a particular lipid type. For LDL: HbA_{1c} at <8.0% 25 fewer measurements; at 8.0% to <9.0% 38 fewer measurements; ≥9.0% 71 fewer measurements; weight status normal, 67 fewer measurements; overweight, 50 fewer measurements; obese, 15 fewer measurements than given in the legend. For HDL: HbA_{1c} at <8.0% 2 fewer measurements; at 8.0% to <9.0% 0 fewer measurements; at ≥9.0% 4 fewer measurements; weight status normal, 6 fewer measurements; overweight, 0 fewer measurements; obese, 0 fewer measurements than given in the legend.

Table 2—Factors predicting change in lipids

Factor	Slope*	95% CI	*P* value
Factors predicting change in LDL (4,299 measurements from 571 subjects)			
HbA_{1c} (per 1%)	Depends on age†		
10 years old	1.9	(0.8, 2.9)	<0.001
18 years old	3.9	(3.2, 4.6)	<0.001
25 years old	5.7	(4.7, 6.7)	<0.001
zBMI (child)‡	Depends on age§		
10 years old	2.1	(−0.6, 4.8)	0.12
15 years old	5.5	(3.7, 7.3)	<0.001
19 years old	8.2	(6.0, 10.4)	<0.001
zBMI (adult)‡	10.4	(8.2, 12.7)	<0.001
Female	2.6	(−1.2, 6.4)	0.18
Nonwhite	−6.5	(−13.7, 0.8)	0.08
Medication	−19.1	(−23.8, −14.4)	<0.001
Supplement	−5.3	(−12.0, 1.4)	0.12
Factors predicting change in HDL (4,428 measurements from 572 subjects)			
HbA_{1c} (per 1%)	0.4	(0.1, 0.7)	0.01
zBMI (child)‡	−1.6	(−2.4, −0.8)	<0.001
zBMI (adult)‡	−3.4	(−4.6, −2.2)	<0.001
Female	5.6	(3.9, 7.4)	<0.001
Nonwhite	2.5	(−0.5, 5.6)	0.11
Factors predicting change in non-HDL (4,421 measurements from 572 subjects)			
HbA_{1c} (per 1%)	Depends on age†		
10 years old	2.2	(0.8, 3.5)	0.004
18 years old	6.6	(5.7, 7.6)	<0.001
25 years old	7.5	(6.3, 8.8)	<0.001
zBMI (child)‡	Depends on age§		
10 years old	4.6	(1.9, 7.3)	0.002
15 years old	7.1	(5.2, 8.9)	<0.001
19 years old	9.1	(6.7, 11.4)	<0.001
zBMI (adult)‡	11.9	(9.6, 14.3)	<0.001
Female	2.2	(−1.9, 6.3)	0.30
Nonwhite	−6.8	(−14.7, 1.0)	0.09
Medication	−11.7	(−16.5, −7.0)	<0.001
Supplement	−5.2	(−12.0, 1.7)	0.14

*Change in lipid (LDL, HDL, or non-HDL) level (mg/dL) per unit change in the indicated factor. †Due to significant interaction, the HbA_{1c} slope varies by age. Estimated slopes are given for subjects at 10, 18, and 25 years of age. ‡Different formulas were used to calculate the zBMI for children and adults. The slope was therefore modeled separately for these groups. §Due to significant interaction, the zBMI slope varies by age for children. Estimated slopes are given for subjects 10, 15, and 19 years of age.

normative values (an increase of 1 in zBMI), LDL increased significantly more as subjects aged from 2 mg/dL to >10 mg/dL. A 1-SD increase in BMI (an increase of 1 in zBMI) was associated with a mean LDL increase of only 2.1 mg/dL when subjects were 10 years old, but increased to a mean of 8.2 mg/dL when subjects were 19 years old. The modification effect of age on HbA_{1c} or zBMI did not differ by a subject's sex.

As expected, medication use was associated with the largest decrement in LDL (19.1 mg/dL). There was no significant effect of prescription of supplements, sex, or ethnicity on LDL.

Table 2 also reports the adjusted associations of HbA_{1c} and zBMI with HDL. Increases in zBMI were associated with significant but modest decreases in HDL (a 1.6 mg/dL decrease in HDL in youths and a 3.4 mg/dL decrease in adults for every 1-SD increase in BMI) (Table 2). Increases in HbA_{1c} level were associated with very small increases in HDL level (a 0.4 mg/dL increase in HDL for every 1% increase in HbA_{1c}). The impact of HbA_{1c} and zBMI on changes in HDL was linear and constant as subjects aged (i.e., no interaction between HbA_{1c} or zBMI and age). Medication or supplement prescription did not impact HDL. Females had significantly greater HDL levels than males, and race/ethnicity did not significantly influence HDL levels.

Table 2 also reports the unadjusted associations of HbA_{1c} and zBMI with non-HDL. HbA_{1c} and zBMI similarly related to LDL and non-HDL. After adjusting for sex and race/ethnicity, our models demonstrated that age modified the relationship between changes in HbA_{1c} and zBMI and changes in non-HDL level (Table 2) with a magnitude similar to that of LDL levels. Our models estimated that medication use led to an ~12 mg/dL drop in non-HDL level. There was no significant effect of supplement use, sex, or ethnicity on non-HDL level.

Figure 2*A* shows the modeled influence of HbA_{1c} on LDL levels as subjects age, and Fig. 2*B* shows the modeled influence of zBMI on LDL levels as subjects age. Both figures demonstrate the greater dispersion in LDL levels according to HbA_{1c} level or zBMI as subjects progress from childhood into adulthood. Because the relationship between HbA_{1c} or zBMI and HDL was predicted to be constant as subjects aged, we do not include a graphic illustration of this relationship as a part of Fig. 2, but it is included in Supplementary Fig. 2. Figure 2*C* and *D* show the modeled influence of HbA_{1c} and zBMI, respectively, on non-HDL levels as subjects age. As for LDL, these figures demonstrate the greater dispersion in LDL levels according to HbA_{1c} level and zBMI as subjects progress from childhood to adulthood.

Sensitivity Analyses

Regression results were similar when the total number of measurements for a subject was included as a covariate (data not shown). Results from a sensitivity analysis restricting each subject to one value per year (data not shown) were also similar. For the model predicting change in LDL, results were unchanged when calculated LDL values were only analyzed if triglyceride concentrations were <200 mg/dL.

CONCLUSIONS

In summary, this article describes the trajectories of LDL, HDL, and non-HDL cholesterol levels in a cohort of youths with type 1 diabetes as they age from childhood into young adulthood. Our

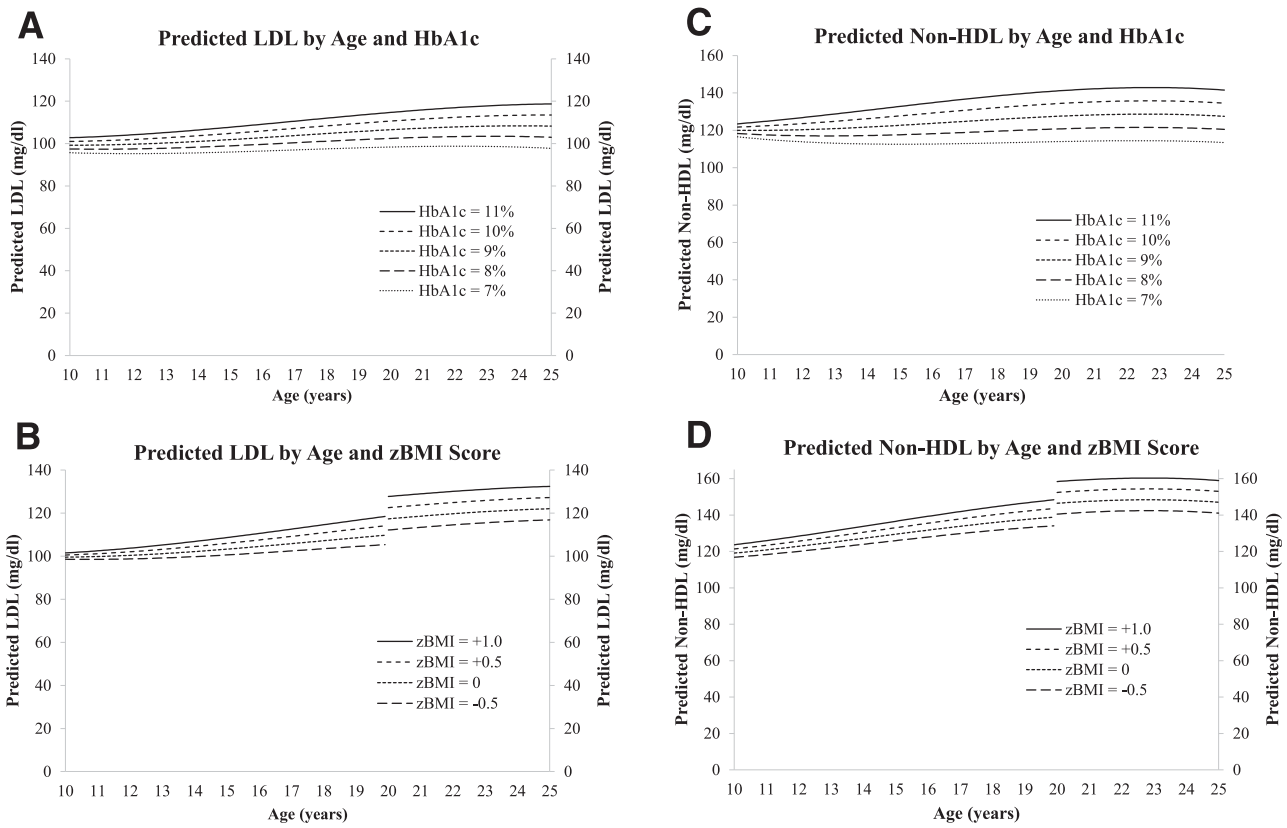

Figure 2—*A*: The modeled changes in LDL levels as subjects age by different HbA_{1c} levels. *B*: The modeled changes in LDL levels as subjects age by different zBMI values. *C*: The modeled changes in non-HDL levels as subjects age by different HbA_{1c} levels. *D*: The modeled changes in non-HDL levels as subjects age by different zBMI values. The zBMI curves are discontinuous at 20 years of age because of differences in how zBMI values are calculated after 20 years of age.

data demonstrate modest increases in LDL and non-HDL cholesterol with increases in HbA_{1c} and zBMI across all ages studied. Notably, increases in HbA_{1c} and zBMI have a greater effect on LDL and non-HDL cholesterol as subjects age. We demonstrate that HDL level decreases with increasing zBMI and that changes in HbA_{1c} have a limited effect on HDL levels.

The negative effects of elevations in childhood lipid levels have been well established. Large cohort studies (23,24) of youths and young adults without type 1 diabetes demonstrate the strong tracking of childhood cholesterol values into young adulthood. Previous research also demonstrates that childhood cholesterol levels impact adult atherosclerosis because childhood LDL levels have significantly predicted adult carotid intima media thickness (25,26). Further, cardiovascular risk factors, including LDL levels, assessed in young adults correspond with coronary artery calcification 15 years later as well or better than contemporaneous assessments of cardiovascular risk (27), demonstrating the importance of addressing cardiovascular risk factor management in youths and young adults.

LDL cholesterol levels have been previously shown to relate to HbA_{1c} and zBMI in youths with type 1 diabetes (28,29). In a 2-year study (14) of youths with type 1 diabetes, longitudinal models predicted improvements in LDL cholesterol levels with improvements in HbA_{1c} levels that were more pronounced in youths with a higher HbA_{1c} level. Another study (29) of 46 youths with type 1 diabetes who were observed over at least 3 years demonstrated increasing LDL levels with increasing zBMI and HbA_{1c} level. Non-HDL level has also been previously shown to relate to HbA_{1c} level and zBMI in youths with type 1 diabetes in cross-sectional analyses (30), and only to HbA_{1c} level in a longitudinal analysis (31). We have added to this literature by examining these associations in a large cohort of youths as they age into adolescence and young adulthood. Additionally, we have included lipid-lowering medication and supplement use in our models.

Our models demonstrate that large changes in HbA_{1c} levels and zBMI values are needed to influence cholesterol levels and that, in childhood, the same decrement in HbA_{1c} or zBMI yields significantly smaller improvement in LDL and non-HDL cholesterol levels than it would in young adulthood. Guidelines often recommend lifestyle change, including weight loss in overweight or obese youths (8) and improvements in glycemic control (9), in addition to specific nutritional changes, such as limiting saturated fat intake, as the initial management of elevated LDL levels in youths with type 1 diabetes. However, our results suggest the degree of improvement in HbA_{1c} levels or zBMI values needed to substantially influence LDL cholesterol levels may not be achievable for many youths and may be especially difficult to achieve for the youngest pediatric patients.

Our study does have limitations. As an observational study, there is the risk of confounders that were not accounted

for in our analyses. The racial diversity in our cohort was limited. The laboratory values that we assessed were obtained as a part of clinical care at irregular intervals, and individuals with higher LDL levels had values obtained more frequently. We accounted for this by adjusting for the number of laboratory values in our models in a sensitivity analysis. Additionally, we completed a sensitivity analysis limited to annual cholesterol measurements in order to create more regular spacing of lipid values, and the results were unchanged. Although pediatric guidelines continue to recommend fasting lipid measurement (8), lipid panels were also often obtained as nonfasting samples, which may have impacted our analyses. However, the results for non-HDL cholesterol and LDL cholesterol levels were quite similar, and non-HDL level is not influenced by fasting status. Further, epidemiologic studies in youths and adults suggest that LDL cholesterol is affected only minimally by fasting status (21,32). We do not analyze triglyceride levels because of concerns over the impact of fasting status on these levels. Theoretically, as these lipid values were obtained as a part of clinical care, clinical lifestyle recommendations could have influenced lipid trajectories but a careful analysis of the effectiveness of such counseling (33) demonstrates that this was not the case. Although the laboratory methods for HbA_{1c} measurement were calibrated to agree with each other, the methodology for HbA_{1c} measurement changed during the study, and this could potentially influence our model results.

In summary, LDL and non-HDL cholesterol levels relate similarly to HbA_{1c} and zBMI in our population of youths and young adults with type 1 diabetes. Increases in HbA_{1c} levels and zBMI values are associated with modest increases in LDL and non-HDL cholesterol levels. There are greater effects of HbA_{1c} levels and zBMI values on LDL and non-HDL cholesterol levels as subjects age, but the influence of HbA_{1c} level and zBMI values on HDL level are constant as subjects age. As an observational study, our study is limited by changes in laboratory methodology, differences in laboratory measurement intervals between subjects, differences in fasting status, and unmeasured confounding. Although this study provides needed context to the management of dyslipidemia in childhood, it cannot answer the important, unanswered questions related to the degree to which dyslipidemia influences later cardiovascular risk in youths and young adults with type 1 diabetes, or to the optimal timing, method, and effectiveness of management for dyslipidemia in pediatric diabetes. Interventional research, such as the currently ongoing AdDIT study, that treats select youths with type 1 diabetes with statins is promising (34), but more research on dyslipidemia management in pediatrics in general and pediatric diabetes in particular is needed (35) so that providers can progress from measuring and tracking lipid levels in youths with type 1 diabetes to effectively providing evidence-based management for dyslipidemia when it occurs.

Acknowledgments. The authors thank the following individuals for their chart review efforts: Lola Adekunle, Charumathi Baskaran, Julia Cartaya, Anita Kao, Roxanne Phillips, and Gabriela Telo (Joslin Diabetes Center, Boston, MA).

Funding. This work was supported in part by grants from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award numbers K12DK094721 and P30DK036836, the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number K23HL125976, the Katherine Adler Astrove Youth Education Fund, the Maria Griffin Drury Pediatric Fund, and the Eleanor Chesterman Beatson Fund.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or other funding sources.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.L.K. contributed to study design, research and interpretation of the data, and writing of the manuscript. C.R.K. performed the data analysis, interpreted the data, edited the manuscript, and approved the final version of the manuscript. C.E.D. contributed to study design, researched the data, and approved the final version of the manuscript. M.M. performed the data analysis, interpreted the data, and approved the final version of the manuscript. L.M.B.L. contributed to study design, data interpretation, and editing the manuscript. M.L.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at ESPE 2013—the 9th Joint Meeting of Paediatric Endocrinology, Milan, Italy, 19–22 September 2013, and at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014.

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